

Faecal calprotectin in suspected paediatric inflammatory bowel disease: an individual patient data meta-analysis

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ABSTRACT

Objectives: The diagnostic accuracy of faecal calprotectin (FC) concentration for paediatric inflammatory bowel disease (IBD) is well described at the population level, but not at the individual level. We reassessed the diagnostic accuracy of FC in children with suspected IBD and developed an individual risk prediction rule using individual patient data.

Methods: MEDLINE, EMBASE, DARE, and MEDION databases were searched to identify cohort studies evaluating the diagnostic performance of FC in paediatric patients suspected of having IBD. A standard study level meta-analysis was performed. In an individual patient data meta-analysis we reanalysed the diagnostic accuracy on a merged patient dataset. Using logistic regression analysis we investigated whether and how the FC value and patient characteristics influence the diagnostic precision. A prediction rule was derived for use in clinical practice and implemented in a spreadsheet calculator.

Results: According to the study level meta-analysis (9 studies, describing 853 patients), FC has a high overall sensitivity of 0.97 (95% confidence interval 0.92 to 0.99) and a specificity of 0.70 (0.59 to 0.79) for diagnosing IBD. In the patient level pooled analysis of 742 patients from 8 diagnostic accuracy studies, we calculated that at a FC cut-off level of 50 µg/g there would be 17 % (95% confidence interval 15 to 20) false positive and 2% (1 to 3) false negative results. The final logistic regression model was based on individual data of 545 patients and included both FC level and age. The area under the ROC curve of this derived prediction model was 0.92 (95% confidence interval 0.89 to 0.94).

Conclusions: In high prevalence circumstances, FC can be used as a non-invasive biomarker of paediatric IBD with only a small risk of missing cases. To quantify the individual patients' risk, we developed a simple prediction model based on FC concentration and age. Although the derived prediction rule cannot substitute the clinical diagnostic process it can help in selecting patients for endoscopic evaluation.

Key words: inflammatory bowel diseases; leukocyte L1 antigen complex; meta-analysis as topic; infant; child; adolescent

ACCEPTED

Introduction

As many as 25% of all IBD cases present in childhood. Given the impact of the disease and its therapy, a reliable and timely diagnosis is mandatory (1). However, the reference standard, endoscopic evaluation with biopsies (2), is invasive, not without risks, and also costly.

Faecal calprotectin (FC) has been investigated as a surrogate marker of neutrophil influx into the bowel lumen and a non-invasive diagnostic test for IBD (3, 4).

van Rheenen and co-workers (5) published a study-level meta-analysis on the diagnostic accuracy of FC for IBD in both children and adults. Based on the calculated summary estimates for specificity, sensitivity and likelihood ratios they concluded that the test is a useful screening tool for identifying those patients most likely needing endoscopic evaluation.

A key problem is however that this meta-analysis was based on aggregate data and did not account for different cut-off levels or different patient characteristics (6).

By contrast, individual patient data (IPD) meta-analysis allows using the original test results as continuous data rather than as dichotomous classification data. In addition, the effect of patient characteristics on test accuracy can be evaluated and quantified (6, 7).

We undertook the current study to update the study-level meta-analysis on the diagnostic performance of FC for paediatric IBD and to complement it with an individual-level meta-analysis. We also sought to develop a prediction model for IBD based on calprotectin level and readily available patient variables.

Materials and Methods

The research was conducted in accordance with the Code of Conduct for Medical Research of the Dutch Federation of Biomedical Scientific Societies (8).

Identification, selection and appraisal of the relevant studies was carried out independently, by two reviewers (PLJD, MPAB). Disagreements were resolved through discussion.

Search methods for identification of studies

A systematic search was performed initially from inception to December 2010 in MEDLINE (Ovid), EMBASE (Ovid), the Database of Abstracts of Reviews of Effects (DARE) of the Centre for Reviews and Dissemination (9) and the MEDION database of the University of Maastricht (10). The electronic search was last updated on April 1, 2012. We refrained from using a diagnostic search filter (11, 12) or language restrictions. Details of the search are given in an online-only document (eText 1, <http://links.lww.com/MPG/A396>). Duplicate articles identified in both Medline and Embase were manually deleted. The reference lists of selected studies were checked for further relevant studies.

Study selection

Only cohort studies evaluating the diagnostic performance of FC concentration in paediatric patients suspected of having IBD were considered for review. Other study designs, such as case-control, are indeed prone to spectrum bias (13). In addition, the following inclusion criteria were applied: FC measurement and reference standard available for all paediatric participants (or a follow-up period long enough to exclude IBD), and sufficient data to calculate 2 x 2 tables.

Data abstraction

The following data were extracted from each study on a pre-designed form: the spectrum of the studied population (indication for testing, age and gender), details of the index and reference test, and counts in the 2 x 2 table.

Individual patient data sets

For the IPD meta-analysis, we contacted the authors of the selected studies and invited them to share the raw, de-identified study data (FC level, age, sex, and final diagnosis). The raw

data were checked for internal consistency against the summary results published in the original paper. Some small discrepancies were found, discussed with the authors and ascertainable divergences were corrected.

Quality assessment

The quality of the included studies was assessed using the revised QUADAS tool (14). Since the calprotectin assay is an objective measurement, 3 of 14 items were omitted: blinded interpretation of the index test, availability of clinical data, and reporting of uninterpretable results. Two reviewers independently answered the 11 remaining questions in the affirmative, in the negative or as being unclear.

Data synthesis and (statistical) analysis

Literature-based meta-analysis:

The aggregate data meta-analysis was performed in Stata/SE version 11.2 (Stata Corporation, College Station, TX, USA) using the Midas command (15). Accordingly, summary statistics for all diagnostic performance indices were calculated within the bivariate mixed-effects logistic regression modelling framework. Between-study heterogeneity of the results was assessed graphically by using forest plots of the diagnostic odds ratios, and statistically by using the χ^2 test of homogeneity and the inconsistency index (I^2). (16) An I^2 value greater than 50% was taken to indicate significant heterogeneity. The potential for publication bias was estimated by using a Deeks' funnel plot. As recommended, a p-value < 0.1 was considered statistically significant (17). A hierarchical summary receiver operating characteristic graph with 95% confidence region and 95% prediction region was constructed.

Individual patient-based meta-analysis:

Although we largely prefer the analytical approach using logistic regression, we also evaluated the diagnostic performance of FC based on the merged individual data. The diagnostic performance was calculated through the MedCalc software, version 11.5.01. (MedCalc Software, Mariakerke, Belgium).

Logistic regression analysis – predicted probability:

The contribution of calprotectin concentration and age, as continuous variables, and gender and study as categorical variables, to the diagnosis of IBD was explored using stepwise forward (likelihood ratio) binary logistic regression analysis. The logit and logistic command in Stata/SE 10.1 were used. An entry probability for each variable was set at 0.05. A clinical prediction rule was derived from the final regression model (see eText 1, <http://links.lww.com/MPG/A396>, for calculation details).

Results

Description of studies

Our search (see Figure 1) returned 161 citations. After removal of 36 duplicates and because 104 of the abstracts were considered not pertinent, 23 records were retrieved as full texts. An additional 4 studies were excluded because of the inappropriateness of the population studied. Insufficient information was available for constructing a 2-by-2 table from 3 studies. Eventually, eight cohort studies fulfilled the inclusion criteria (18-25). A ninth relevant population-based cohort study was discovered in a recently published diagnostic meta-analysis (5). The original study (26) does not provide data to construct a 2x2 table, but the meta-analysis does.

The authors of eight cohort studies (18-25) were willing to share a data set with individual patient data (age, gender, calprotectin concentration, and final diagnosis). Age and gender

were not available from the Diamanti et al. study due to a computer crash. The authors of the Ashorn et al. paper (Dr. Kolho) provided data on 31 additional patients recruited after publication of their study results (18). In the most recently published study (25) not all patients underwent endoscopy, but a sufficiently extended follow-up period (disease free period of 6 months) should minimize the risk of verification bias (27). To completely eliminating this type of bias, we excluded the 43 patients without histologically confirmed IBD from the IPD meta-analysis. The Norwegian group (26) justified their refusal by arguing that the data will again be used for their own follow-up study. None of the authors is aware of missed (un)published diagnostic accuracy studies fulfilling the selection criteria.

Characteristics of included and excluded studies

All nine included cohort studies (18-26) were undertaken in referral centres for paediatric gastroenterology and involved 853 patients from the toddler age group to young adults. Table 1 summarizes the characteristics of the study population, a description of the applied index and reference tests, and the findings. In one study (19) four patients were excluded because infectious gastroenteritis was the final diagnosis. Upon enquiry, none of the authors were aware of similar patients in whom readily available diagnostic investigation could have prevented unjustified study entry and unnecessary false positive or true negative cases. Another study (24) contained 16 patients whose calprotectin results were expressed as greater or less than a numerical value. These test results were substituted by a value midway between the reported numerical value and a higher or lower value present in the data set. This procedure is unlikely to influence the test accuracy parameters since 14 of the 16 adjusted values were situated in the highest or lowest quintile. The bar graph in eFigure 1 (<http://links.lww.com/MPG/A395>) is a representation of the quality of the 9 selected cohort studies (18-26).

Summary results for all included studies

Literature-based meta-analysis:

A summary of test accuracy estimates is shown in Table 2. The Cochran Q test and the I^2 values are indicative for substantial heterogeneity (28). Figure 2 shows a forest plot of the diagnostic odds ratio and the pooled estimate for the 9 cohort studies (18-26). The average prevalence of IBD in the cohort studies was 0.54. Accordingly, the post-test probability of a positive calprotectin test could be estimated to be 0.79 (95% CI 0.72-0.85). The post-test probability of a negative calprotectin test is 0.05 (0.01-0.14).

Figure 3 shows the hierarchical summary receiver operating characteristic (HSROC) graph with 95% confidence region and 95% prediction region.

Publication bias was assessed by Deeks' funnel plot asymmetry test for small study effect/publication bias. The non-significant slope ($p=0.62$) indicates that no significant bias was found.

Individual patient-based meta-analysis:

Individual patient data on final diagnosis and FC were collated from 742 children from 8 studies (18-25). The studies were significantly different with respect to age ($p=0.004$, one-way ANOVA test), mean FC concentration ($p<0.001$, one-way ANOVA test), and area under the ROC curve ($p=0.001$, one-way ANOVA). The pre-test probability ranged from 0.51 (95% CI 0.39-0.63) to as high as 0.84 (0.75-0.90).

In the pooled data set of all children the “optimal” cut-off value (the value with the highest accuracy – minimal false negative and false positive results) for FC was 212 $\mu\text{g/g}$ corresponding with a sensitivity of 0.90 (95% CI 0.87-0.93), a specificity of 0.85 (0.81-0.88), a positive likelihood ratio of 5.99 (4.6-7.8), and a negative likelihood ratio of 0.11 (0.09-0.20). The area under the receiver operating characteristic (ROC) curve of FC for the diagnosis of paediatric IBD was 0.94 (95% CI 0.92-0.95).

Logistic regression analysis – predicted probability

The results of the logistic regression analysis (eText 1, <http://links.lww.com/MPG/A396>) disclosed that calprotectin concentration, age and study centre were independent predictors of IBD. The influence of study centre (likelihood ratio test significant) confirms heterogeneity across the studies.

Outside the 8 study centres a regression equation containing a term related to the study centre is not of use, therefore the impact of study centre on the diagnosis was omitted from the final regression model: $\text{logit}(p) = S = -3.294 + 0.004 * FC + 0.175 * AGE$, where the explanatory variable FC is the FC concentration in $\mu\text{g/g}$ and AGE is the age in years. The predictivity of this simplified model was evaluated by ROC curve analysis. The estimated area under the ROC curve (AUC) for the final model was calculated to be 0.92 (95% CI 0.89-0.94). The logistic model using calprotectin concentration and age predicts IBD correctly in 85.5% (466/545) of children (sensitivity 0.81 (95% CI 0.76-0.85), specificity 0.92 (0.88-0.95), PPV 0.93 (0.89-0.96) and NPV 0.73 (0.72-0.83).

The probability of having IBD is determined by the equation: $p = \exp(S)/(1+\exp(S))$. We programmed an Excel spreadsheet (eFile1, <http://links.lww.com/MPG/A397>) computing the probability (with CI) of having IBD for each combination of FC, age and disease prevalence. Figure 4 illustrates that assuming a disease prevalence of 56%, a FC of 700 $\mu\text{g/g}$ in a 6 year old child corresponds to an IBD probability of 64% (95% CI: 52-71). This prediction lacks precision and the post-test probability is hardly improved compared to the average pretest-probability. In a 17 year old adolescent the same test result makes the diagnosis quite probable, but ruling out IBD at this age and this pre-test probability is practically impossible.

Discussion

Principal findings

This systematic review has provided an updated aggregate data meta-analysis confirming the high diagnostic accuracy of FC for the detection of IBD in referral centres for paediatric gastroenterology. In addition, a meta-analysis using individual participant data enabled us to develop an algorithm predicting the likelihood that an *individual* child suffers from IBD. It was previously not recognized that the probability of having IBD depends both on the FC level and the age of the child.

General considerations

The literature-based meta-analysis indeed confirms that FC has an excellent overall sensitivity of 0.97 (95% CI 0.92-0.99) and a modest specificity of 0.71 (0.59-0.80) for diagnosing paediatric IBD. A first observation is that, due to the relatively small number of pooled investigated patients, the imprecision of the predictive values is still considerable. In addition, although we used recommended, robust state of the art statistical methodology (29), the estimation of summary points does not hold true if the included studies have used different threshold values (30). For the clinician, it is not evident at which cut-off value the calculated summary estimates of the test accuracy measures apply. Therefore we recalculated the diagnostic performance of FC using merged individual patient data. The “optimal” cut-off for the whole group equals 212 µg/g. Taking into account the pretest probability and the likelihood ratios, the clinician can now better interpret a test result and discuss the predictive value with the patient and his/her parents. We should however realize that the predictive values or likelihood ratios are applicable to the whole group of patients presenting with a test result above or below the threshold and that dichotomizing carries with it a loss of information for the individual child (31). This drawback can be overcome by using logistic

regression analysis, a technique which allows taking into consideration patient-level covariates as well.

The contribution of age in the prediction of IBD turned out to be significant. FC concentrations have been shown to be higher in preschool children, especially infants, than in older children (32, 33). This age-dependency does not seem to play an important role in our logistic regression model since there is no significant correlation between age-quartile and FC in non-IBD subjects ($r = -0.06$; $p = 0.34$). In contrast, the prevalence of IBD is significantly increased with higher age-quartile (Chi-square test, $p < 0.0001$), suggesting that the age factor corrects for the age dependent prevalence.

Our literature search revealed some of the well-known shortcomings in the quality and reporting of diagnostic research (27). We had to exclude nearly half of the paediatric accuracy studies because they used a case-control design known for introducing spectrum bias (13). None of the studies pre-specified a target value for sensitivity, specificity, predictive accuracy and a minimal acceptable lower confidence limit, enabling sample size calculation (34, 35). Admittedly, neither did we define a target region within which the summary estimates of our meta-analysis should fall. We suggest that the absence of a predefined target makes authors all too often undeservedly enthusiastic about the diagnostic value of an index test.

Our meta-analysis differs in some aspects from the study of van Rheenen and co-workers (5). They included one study which we excluded (36) whereas we added three new studies totalling 404 participants (20, 22, 25). Doctor Golden (personal communication – 03-18-2010) discouraged us from using her group's data (36) because Magne Fagerhol's original assay, measuring calprotectin as mg/L assay buffer, does not correlate very well with the new commercial assays expressing the results as $\mu\text{g/g}$ faeces.

The major difference between van Rheenen's (5) and this paper is the IPD meta-analysis. As already known, the collection of individual patient data is time consuming and difficult. A high level of persuasiveness was needed to collect the raw study data from 8 of the 9 cohort

studies. Consequently, we were able to use easily available patient characteristics and the original continuous calprotectin data instead of the dichotomized study results in a logistic regression analysis.

It is also noteworthy that we detected and were able to correct small discrepancies between the raw data and the published data.

By publishing all the available raw data (eTable 1, <http://links.lww.com/MPG/A398>), we comply with the appropriate and growing request to share complete data, allowing re-analysis by the reader and sequential meta-analysis if new studies appear. There is indeed a growing awareness that sharing data is an ethical obligation (37-42).

Strength of the study

Compared to the systematic review of van Rheenen et al. (5), the key strength of our study is the IPD meta-analysis. Although a literature-based meta-analysis provides a good overall impression of the diagnostic accuracy of the test, pooling of studies with different diagnostic thresholds (from 50 to 160 µg/g faeces) precludes the calculation of the predictive value at a self-selected threshold or the patient's result. Only IPD permits prediction based on numerical test results and adjustment for patient characteristics. Our prediction tool calculates an individualized disease risk with accompanying confidence range taking into account the FC concentration and the patient's age. In a paediatric gastroenterology referral centre, ruling out IBD is difficult in older children, whereas in younger patients a higher FC concentration is needed to get a post-test probability larger than the prevalence.

Study weaknesses

Our search methodology aimed to avoid language and citation bias but we cannot exclude publication or reporting bias in our meta-analysis. Publication bias is probably even more of a

problem for diagnostic and prognostic than for therapeutic studies (43, 44). The effects of reporting bias in therapeutic meta-analyses have recently been shown to be substantial (45). Our IPD meta-analysis may also suffer from availability bias. Data from two large studies are incomplete or unavailable. In this context, it is noteworthy that the study of Perminow et al. (26) was not intended to be a diagnostic accuracy study and showed the lowest diagnostic odds ratio.

We also recognize that the number of patients in the meta-analysis is still limited. Therefore the precision of the diagnostic accuracy measures and our predictive algorithm leaves room for improvement. Furthermore, the final logistic regression equation contains only two independent variables. This likely represents an oversimplification of a complex clinical diagnostic process, including information collected during history taking and physical examination. The user of the algorithm should be aware of this. Other laboratory test results, such as CRP, haemoglobin, and iron indicators, could improve diagnostic precision but were not available for this study. Clinical suspicion or “gut feeling” may also be of additional diagnostic value.

Finally, the between-study heterogeneity is of concern and not fully understood. Although the selection criteria are more or less the same (suspected inflammatory bowel disease), between-study differences were shown for age and FC concentration. The prevalence of IBD varied from 51% to 84%, and the false positive rate ranged from 0 to 29% suggesting dissimilar study entry criteria. We have also noticed that there was a negative, just significant linear correlation ($r = -0.71$, $P=0.049$) between prevalence and the false positive rate.

Differences in clinical laboratory measurement procedures for FC may be another source of heterogeneity (46). We know that even small analytic biases can indeed shift the laboratory values and lead to diagnostic misclassification (47, 48).

Implications for clinical practice and future research

Despite the absence of validation, and given the mentioned concern about study heterogeneity and (reporting) bias, our predictive algorithm is currently the best available tool for predicting IBD in the individual child. As such it deserves a valid place in the decision making process. We nevertheless advocate a large prospective multi-centre study to improve and refine the IBD screening tool. More data are needed to validate the prediction algorithm on a different data set to improve its precision. Every effort should be made to standardize and harmonize calprotectin measurements and the predictive value of other clinical variables and (faecal) biomarkers (49, 50) should be investigated simultaneously.

Conclusion

Using an IPD meta-analysis and through regression modelling we identified FC concentration and age as independently associated with the diagnosis of IBD. We developed a prediction rule that enables the practicing paediatric gastroenterologist to numerically interpret the FC value together with the patient's age. As such, this rule can be a valuable adjunct to the diagnostic armamentarium making physician and patients/families better equipped to make personalized decisions.

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Figure, Table Legends and Supplemental Data

Figure 1. Flowchart showing the search for and selection of papers evaluating faecal calprotectin in children with suspected inflammatory bowel disease. The final search was carried out on April 1st, 2012

Figure 2. Forrest plot of diagnostic odds ratio of each individual cohort study, pooled odds ratio, Cochran Q test heterogeneity and I^2 statistic for inconsistency.

Figure 3. Summary ROC space of sensitivity and specificity for faecal calprotectin in the diagnosis of paediatric IBD. The circles depict the observed bivariate pairs of sensitivity and specificity of the 9 diagnostic cohort studies (18-26). The blue solid line is the summary ROC curve. The diamond is the bivariate summary point. The red dashed line triangle is the bivariate boundary of the 95% confidence region for the bivariate summary point and the green dotted line encloses the 95% prediction region. The study numbers correspond to those reported in Table 1.

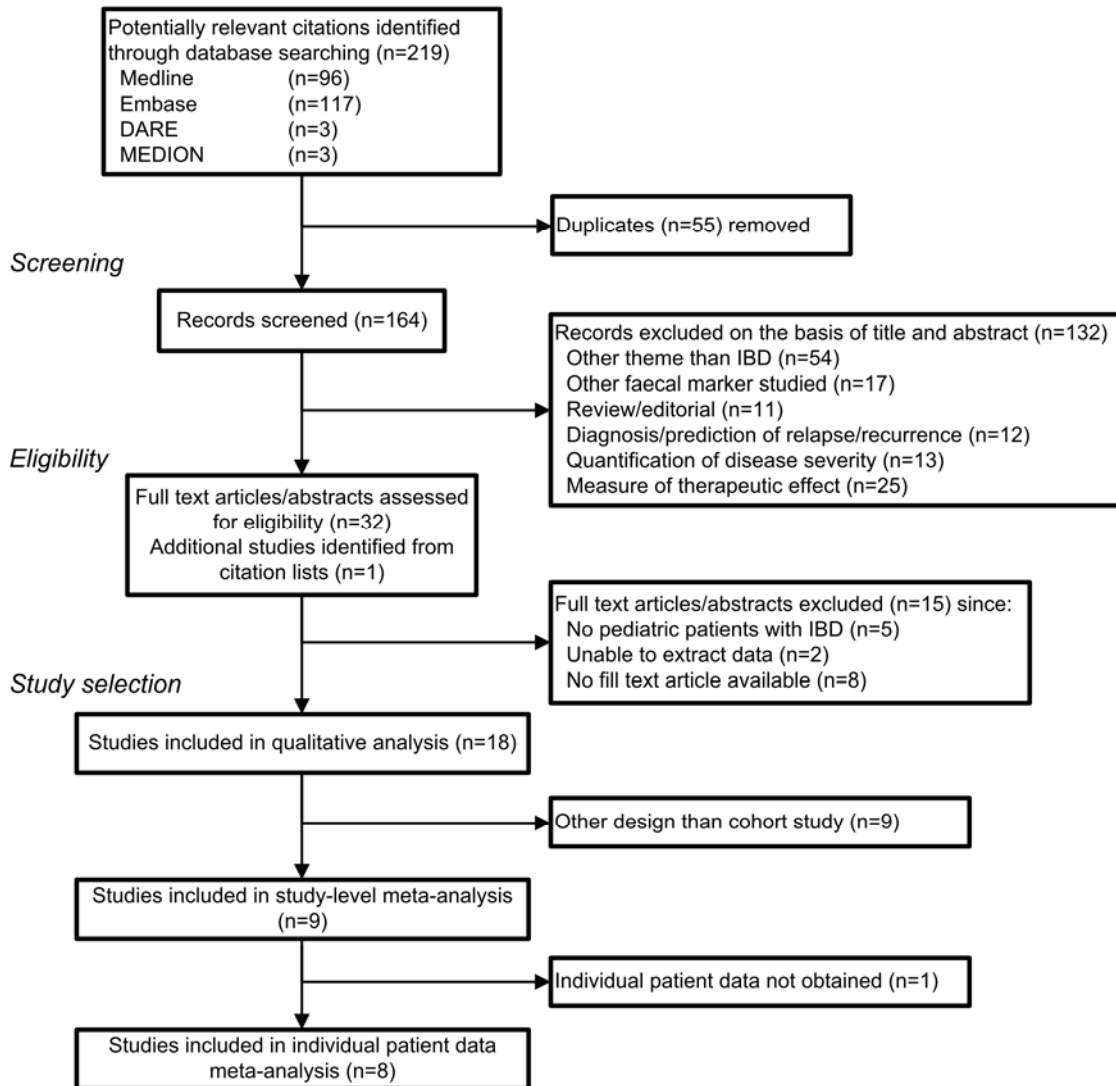
Figure 4. Plots of the predicted probabilities as a function of faecal calprotectin concentration, age and disease prevalence. This figure illustrates that age has an important additional value to calprotectin testing for the diagnosis of IBD. UL: upper limit of 95% CI, LL: lower limit of 95% CI

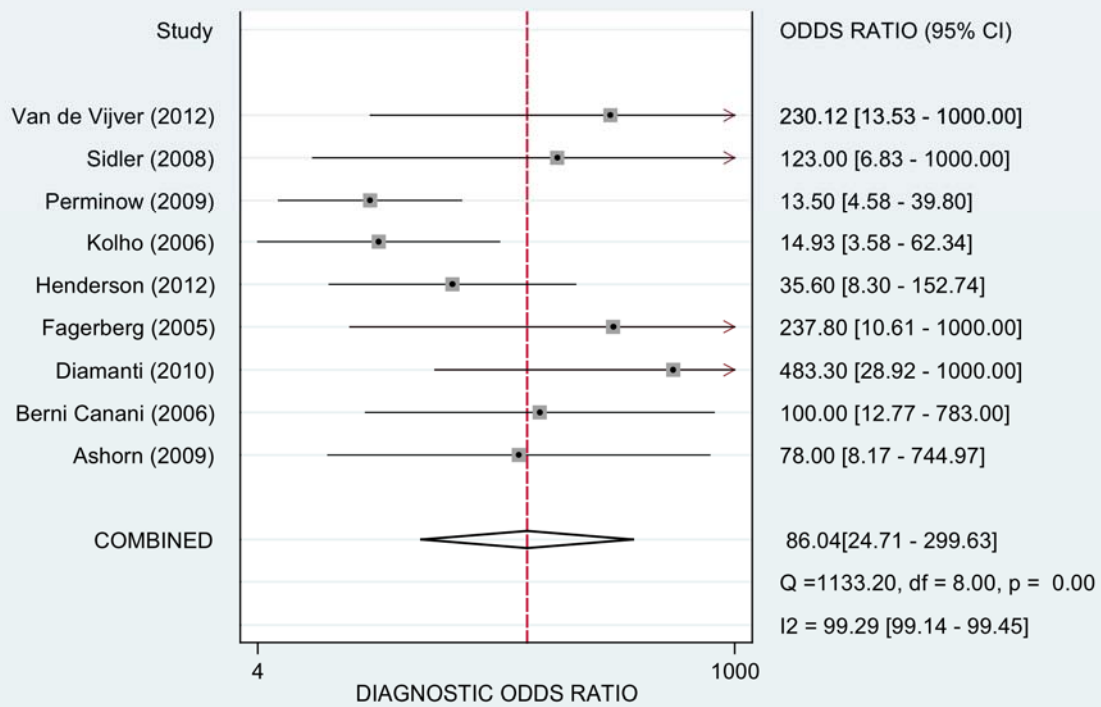
Table 1. Characteristics and 2 x 2 data of all included studies. TP: true positive, FP: false positive, FN: false negative, TN: true negative

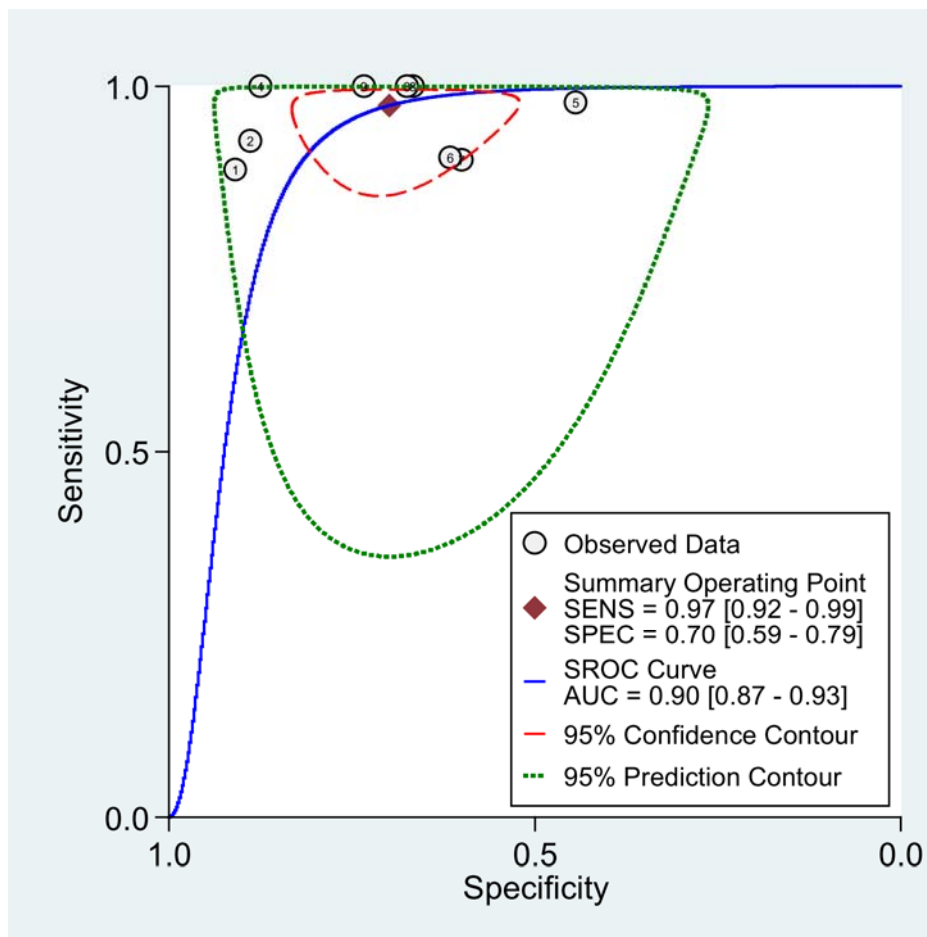
Table 2. Numerical results of the literature-based meta-analysis (faecal calprotectin for the diagnosis of IBD): test performance parameters and their 95% CI. DOR: diagnostic odds ratio, LR+: likelihood ratio of a positive test, LR-: likelihood ratio of a negative test.

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Identification







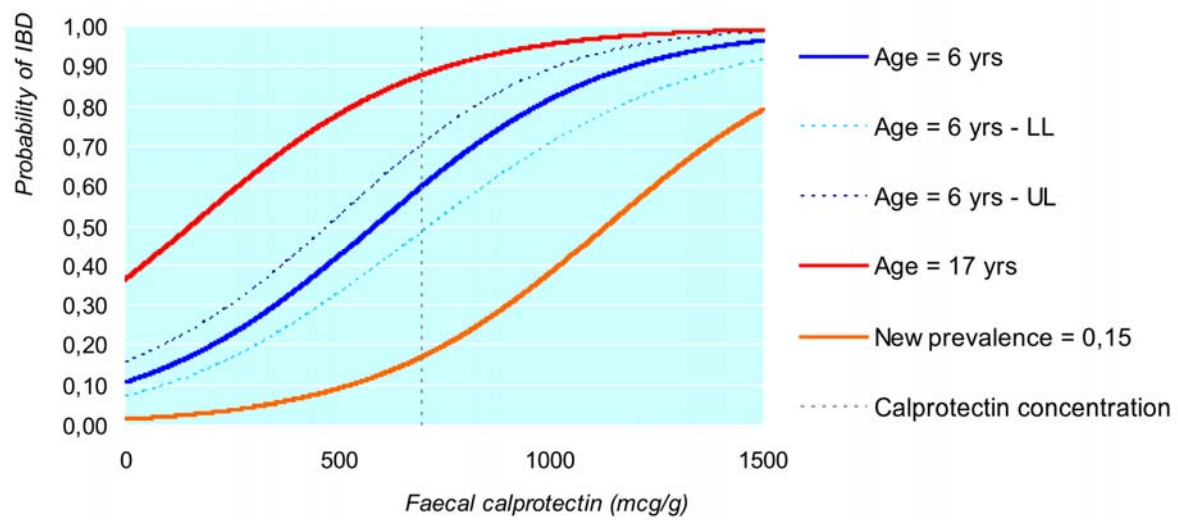


Table 1. Characteristics and 2 x 2 data of all included studies

Study, year (reference)	Patient characteristics				Index test	Cut-off value (µg/g)	Reference test	Prev	TP	FP	FN	TN
	Setting, location	Spectrum	Age range or mean(sd) (yrs)	Female/ male (n)								
1 Ashorn et al, 2009 ²⁰	Children's Hospital, University of Helsinki, Finland	Suspicion of IBD	5.8-19.9	50	Phical Test	100	Histopathology	0.80	39	1	5	10
								0.84	62	1	10	13
2 Berni Canani et al, 2006 ²¹	Paediatric Gastroenterology Unit; Naples, Italy	Children referred for initial assessment of suspected IBD	Non-IBD 11.0(3.3) CD 14.5(5.1) UC 11.0(5.0)	21/24	Calprest®	95.3	Standard diagnostic criteria, including histopathology	0.60 ↓ 0.66	25	2 ↓ 0	2	16 ↓ 14
3 Diamanti et al, 2010 ²²	Paediatric Gastroenterology and Nutrition Unit, Rome, Italy	Children referred for recurrent abdominal pain and altered bowel habits	Non-IBD 1-18 IBD 1-18	88/109	Calprest®	100	Histological examination	0.59	117	26	0	54
						160		0.59	117	16	0	64
4 Fagerberg et al, 2005 ²³	Department of gastroenterology, Stockholm and Paediatrics, Västerås, Sweden	Scheduled for colonoscopy to rule out IBD; no bacterial gastroenteritis	IBD 6.7-17.8 Non-IBD 6.5-17.3	19/17	Calprest®	50	Conventional histopathological criteria for diagnosis of IBD	0.56	20	2	0	14
5 Henderson et al, 2012 ²⁴	Paediatric gastroenterology department, Edinburgh UK	Children evaluated for suspected bowel inflammation	IBD 12.6, IQR: 9.5-14.0 Non-IBD 9.3, IQR: 5.2-12.7	79/111	PhiCal Test	50	Complete endoscopic evaluation + biopsies, small bowel imaging plus follow-up of ≥ 12 months	0.48	89	55	2	44
6 Kolho et al, 2006 ²⁵	Children's Hospital, University of Helsinki, Finland	Children undergoing colonoscopy	0.9-18 9.8(4.7)	29/28	Phical Test	50	Colonoscopy + histology	0.54	28	10	3	16
						100		0.54	27	8	4	18
7 Perminow et al, 2009 ²⁸	South-Eastern Norway	Children with suspected IBD (treatment naïve)	IBD 0.8-17.9 Non-IBD 1.9-18	95	?	160	Histopathological (Porto criteria)	0.63	54	14	6	21
8 Sidler et al, 2008 ²⁶	Gastroenterology Outpatient Clinic, Randwick Australia	Symptoms suggestive of an organic gut disease	Non-IBD 2.2-15.5 IBD 2.4-16	24/37	PhilCal test	50	Standard diagnostic criteria, including histopathology	0.51	31	10	0	20
9 Van de Vijver et al, 2012 ²⁷	Department of Paediatric Gastroenterology, Groningen, Netherlands	Clinical suspicion of IBD	IBD 6-18 Non-IBD: 6-18	61/56	Calpro® elisa test	50	Esophagogastro-duodenoscopy and ileocolonoscopy including histopathological verification or 6 months follow-up	0.36	42	20	0	55

Table 2. Numerical results of the literature-based meta-analysis (faecal calprotectin for the diagnosis of IBD): test performance parameters and their 95% CI along with Cochran-Q and inconsistency. DOR: diagnostic odds ratio, LR+: likelihood ratio of a positive test, LR-: likelihood ratio of a negative test.

Parameter	Estimate (95% CI)	Cochran-Q (P-value)		Inconsistency (I^2) (%) (95% CI)
Sensitivity	0.97 (0.92 to 0.99)	30.21	0.00	73.52 (55.84 to 91.20)
Specificity	0.70 (0.59 to 0.79)	34.33	0.00	76.70 (61.62 to 91.77)
DOR	86 (25 to 300)	1133.20	0.00	99.29 (99.14 to 99.45)
LR+	3.2 (2.3 to 4.5)	39.24	0.00	66.87 (66.87 to 92.36)
LR-	0.04 (0.01 to 0.12)	21.09	0.01	62.06 (34.57 to 89.56)